15. (Amended) A composition for topical administration of 33-epi-chloro-33-desoxy-ascomycin which composition comprises 33-epi-chloro-33-desoxy-ascomycin and a carrier vehicle, said carrier vehicle comprising

(i) means to retain water in the outer skin layer, and

(ii) means to hinder water evaporating from the skin.

REMARKS

Claims 14-41 are pending in the instant application all of which stand finally rejected. Applicants have amended claims 14 and 15 to make it explicit that the ascomycin is part of the composition to be applied to the skin. Applicants submit this is clear throughout the specification, in particular the examples. Accordingly, it is submitted no new matter will be added by entry of the instant amendment. Applicants respectfully request reconsideration of the final rejection in view of the foregoing amendments and following remarks.

The rejection of claims 14-41 under 35 U.S.C. 103(a) as being unpatentable over Asakura et al (US 5,385,907) in view of Baumann et al (US 5,352,671), Treiber et al (US 5,225,403) and Bradley et al (US 6,124,362) is respectfully traversed.

The present invention is directed to compositions for the topical administration of an ascomycin for the treatment of skin disorders. Ascomycins have a variety of useful pharmacological actions, e.g. immunosuppression, which makes them attractive for topical administration. However they have drawbacks which make formulation of effective topical compositions problematic. For example, their physiochemical properties, e.g. high molecular weight and lipophilicity, have posed problems for topical dosage forms. In addition, the skin disorders themselves present difficulties in treatment with topical compositions. Particularly problematic are lichenified skin diseases, e.g. psoriasis, where the skin is hyperproliferated and the skin barrier and skin lipid composition may have changed. The compositions of the instant invention address these problems and, quite surprisingly, serve to enhance penetration of the ascomycin through human skin. Specifically, the compositions of the present invention comprise an ascomycin and a carrier vehicle, the carrier vehicle comprising a means to retain water in the outer skin layer and a means to hinder water evaporating from the skin. It is respectfully submitted that none of the references cited by the Examiner, alone or in combination, teach or suggest the compositions of the instant invention.

Asakura et al is directed to topical compositions comprising specific tricyclic compounds as shown in formula I (column 2) and a solubilizing and/or absorption promoting agent. In column 6, lines 18-21, a solution comprising the compound of formula I or its salt in the solubilizing and/or absorption-promoting agent is formulated with an ointment base. The ointment bases are oil and

fat bases including liquid paraffin, white petrolatum and solid paraffin (column 6, lines 22-30). In addition the ointments of Asakura may contain, among other things, "absorption-promoting agents such as higher alkene carboxylic acid (e.g., oleic acid)" (column 6, lines 31-36). Asakura does not teach or suggest facilitating penetration of the ascomycin by maintaining sufficient moisture on the skin, i.e. by adding a means to retain water in the outer layer.

The Examiner states that "Asakura et al teaches topical preparation including ointments, ...containing derivatives of FK-506 including ascomycin as an active ingredient. It teaches that beneficial carrier system which enhances the absorption and solubility of said active ingredient wherein it includes hydrocarbons (e.g. paraffin, petrolatum, etc), lanolin or waxes and abso[r]ption – promoting agents such as carboxylic acid (oleic acid) or esters thereof." Applicants point out that the only acids described by Asakura et al are higher alkene carboxylic acids e.g. oleic acid. Applicants submit the Asakura et al preparations are distinct from the instant invention.

The instant claim 14 is directed to compositions for topical administration of an ascomycin which comprises an ascomycin and a carrier vehicle, the carrier vehicle comprising (i) a means to retain water in the outer skin layer comprising a urea, an inorganic salt, or a carboxylic acid wherein said carboxylic acid is a carboxylic acid or derivative thereof selected from the group consisting of a cyclic carboxylic acid or salt thereof; lactic acid; glycolic acid; lactic acid sodium and/or ammonium salt; glycolic acid sodium and/or ammonium salt; lactamide; lactamidopropyl-triammonium chloride; and sodium cocoyl lactylate, and (ii)means to hinder water evaporating from the skin. Asakura et al is silent as to the requirement of the instant invention for a means to retain water in the outer skin layer and does not teach any of the specific materials for accomplishing this, i.e. a urea, an inorganic salt, or a carboxylic acid wherein said carboxylic acid is a carboxylic acid or derivative thereof selected from the group consisting of a cyclic carboxylic acid or salt thereof; lactic acid; glycolic acid; lactic acid sodium and/or ammonium salt; glycolic acid sodium and/or ammonium salt; lactamide; lactamidopropyl-triammonium chloride; and sodium cocoyl lactylate. The only acids taught by Asakura et al are higher alkene carboxylic acids and the only specific acid mentioned is oleic acid, which is not encompassed by the instant claim 14.

Applicants respectfully disagree with the Examiner's position that Asakura et al "teaches inclusion of inorganic salts such as sodium salt or potassium salt which increases the solubility of said active agents (salts of the active compound)." In column 4, Asakura et al is referring to salts of the active ingredient itself ("The pharmaceutically acceptable salts of the compound (I) (emphasis added) include conventional non-toxic and pharmaceutically acceptable salts such as the salts with inorganic or organic bases, specifically, an alkali metal salt such as sodium salt or potassium salt"), not about salts as separate components in a galenical composition. This is clearly very distinct from the instant invention wherein the inorganic salt is being added as a

separate component, i.e. as the means to retain water in the outer skin layer. It should be noted that it may not be possible to form salts of all ascomycins. In fact, it is not clear whether salts of 33-epichloro-33-desoxyascomycin , which is neither taught nor suggested by Asakura et al, can form at all. There is no appropriate functional group on the molecule and therefore, addition of e.g. sodium hydroxide, does not easily lead to salt formation.

In view of the foregoing is it clear Asakura et al does not teach or suggest the instant invention. Applicants submit the secondary references, taken individually or together fail to make up for the deficiencies of Asakura et al.

Baumann et al is directed to particular ascomycins per se and specifically, as pointed out by the Examiner, discloses 33-epichloro-33-desoxyascomycin. It does not teach any specific topical formulations. The relevance of the Examiner's statement that Baumann *et al* teaches the use of sodium chloride in the manufacture of ascomycins is not understood. Firstly, it is unclear that Baumann et al teaches the use of sodium chloride in the manufacturing process and secondly, even if it did, it would be irrelevant to the instant invention. The present invention is directed to particular galenical formulations of ascomycins, it is not directed to the manufacture of specific ascomycins. Clearly, there is no motivation to combine Baumann et al with Asakura et al but even if one did, they would not arrive at the instant invention.

Treiber et al is directed to a process for producing a new FK-506 antagonist agent under a fermentation process. In the general disclosure for pharmaceutical preparations comprising the FK-506 antagonist agent (column 7, lines 13-18), Treiber et al describe compounding the active "with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use." Immediately following, Treiber et al lists a number of carriers that can be used in manufacturing the preparations in solid, semi-solid, or liquid form. Urea is one of the listed carriers. Treiber et al is silent as to which particular dosage form urea should be used. There is no mention of ointments, in fact, Treiber et al state the preferable route of administration is by parenteral or enteral administration (column 7, lines 29 –30). Clearly, there is no teaching or suggestion of the instant invention. In addition, there is no motivation to combine Treiber et al with Asakura et al but even if there was, it is not seen how the combination would direct one to the instant invention without the hindsight of the present disclosure.

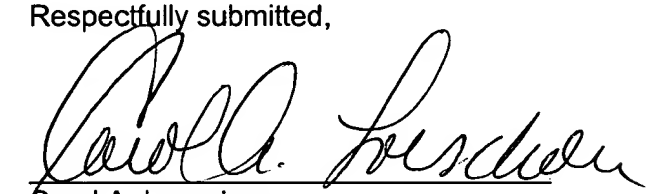
Bradbury et al is directed to methods for regulating hair growth using terpenes optionally in combination was various activity enhancers "chosen from a wide variety of molecules which can function in different ways to enhance the hair growth effects of a compound of the ... invention" (column 22, lines 61-64). The wide variety of activity enhancers mentioned include FK506 analogs (col. 23, line 36) and ascomycin derivatives (col. 25, lines 62 – 63). Urea is mentioned as one of

many penetration enhancers (column 24, line 57). The Examiner also mentions that 2-pyrrolidone-5-carboxylate is listed in column 24 as a penetration enhancer. However, the undersigned didn't see it there. While topical compositions are envisioned therein, it is not skin but scalp that is involved. In addition, while ascomycins are mentioned as one of many possible activity enhancers, and urea one of a list of penetration enhancers, neither is specifically used alone in a Bradbury et al composition and nowhere is there a teaching or suggestion of using the two together in a formulation. Bradbury et al is directed to using terpenes to regulate hair growth. There is no teaching or suggestion of the compositions of the instant invention for treating skin disorders. Further, there is no motivation to combine Bradbury et al with Asakura et al but even if there was it is not seen how the combination would lead to the instant invention.

In view of the foregoing, it is respectfully submitted that the instant invention is patentable over the cited references. Accordingly, reconsideration of the instant application is respectfully requested.

Entrance of the present amendment is believed to place the claims in better condition for allowance or at least reduce the issues for consideration on appeal. Thus, entrance of the amendment in the application and allowance of all claims are respectfully requested.

Respectfully submitted,



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Date: September 9, 2002

MARKED-UP VERSION OF CLAIMS TO SHOW CHANGES MADE

14. (Twice amended) A composition for topical administration of an ascomycin for treatment of skin disorders which composition comprises an ascomycin and a carrier vehicle, said carrier vehicle comprising

(i) means to retain water in the outer skin layer comprising a urea, an inorganic salt, or a carboxylic acid, wherein said carboxylic acid is a carboxylic acid or derivative thereof selected from the group consisting of a cyclic carboxylic acid or salt thereof; lactic acid; glycolic acid; lactic acid sodium and/or ammonium salt; glycolic acid sodium and/or ammonium salt; lactamide; lactamidopropyl-triammonium chloride; and sodium cocoyl lactylate, and

(ii) means to hinder water evaporating from the skin.

16. (Amended) A composition for topical administration of 33-epi-chloro-33-desoxy-ascomycin which composition comprises 33-epi-chloro-33-desoxy-ascomycin and a carrier vehicle, said carrier vehicle comprising

(ii) means to retain water in the outer skin layer, and

(ii) means to hinder water evaporating from the skin.

☒ Enclosed is a Petition for Extension of Time.

Respectfully submitted,

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